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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/533,047	12/14/2005	Rakesh K Jain	00786/433002	9277

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EXAMINER
FORD, ALLISON M

ART UNIT	PAPER NUMBER
1651	

NOTIFICATION DATE	DELIVERY MODE
09/26/2008	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

patentadministrator@clarkelbing.com

Office Action Summary	Application No.	Applicant(s)	
	10/533,047	JAIN ET AL.	
	Examiner	Art Unit	
	ALLISON M. FORD	1651	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *12 June 2008*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-28 and 79-86* is/are pending in the application.

4a) Of the above claim(s) *5,6,19 and 23* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-4,7,9-18,20-22,25-28 and 79-86* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *20070409*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Election/Restrictions

Applicant's response of 6/12/2008 has been received and entered into the application file. Claims 7, 8, 22 and 23 have been amended; new claims 81-86 have been added; claims 29-78 are cancelled.

In response to the election of species requirement, Applicants elected "perivascular cells" as the species of first cell to be administered, "primary culture endothelial cell" as the species of second cell to be administered, and "heart" as the organ or tissue to be treated. The elections were made with traverse. The traversal is on the ground(s) that the requirements for election are inappropriate because there was a disclosed relationship between each of the claimed species, and thus there would be no serious burden placed on the Examiner to consider all species in a single application. Specifically, with regards to the requirement to elect a single cell type from claims 1 and 18, Applicants assert that each of the cell types share the common functional relationship of having the potential to promote formation of a microvascular scaffold. With regards to the requirement to elect a single cell type from claims 7 and 22 (now recited in new claims 83 and 85), Applicants assert that each of the cell types are endothelial or endothelial precursor cells. With regards to the requirement to elect a single species of tissue or organ from claims 15 and 25, Applicants assert that each of the tissues and organs claimed require vascularization for growth and survival.

Applicant's traversal has been fully considered, but is not found persuasive.

It is respectfully submitted that the instant application is a national stage entry under the provisions of 35 USC 371, and thus restriction between inventions and species is based on whether or not there is unity of invention between the different inventions and species, see PCT Rules 13.1 and 13.2. Applicants' reliance on the statements of MPEP § 808.01(a) with regards to burden is therefore not applicable to the instant application. Rather, as set forth in the original requirement for election of

species, under PCT Rule 13.2, requirement to elect a single species is appropriate when the species lack the same or corresponding special technical features. While Applicant has asserted that the species within each grouping do share a common feature, the asserted features are not sufficient to show the species are art recognized equivalents, as required by PCT Rule 13.2 and PCT Administrative Instructions, Annex B, Part 1(f)(I)(B)(2). As was pointed out the original requirement, the disclosed species of the first cell type to be administered represents a wide and varied genus of cells which may share the ability to *potentially promote formation of a microvascular scaffold*, there is no evidence that each of the recited cell species *actually* promote formation of a microvascular scaffold under any common circumstances. The disclosed species of second cell type to be administered still represents a wide and varied genus of cells, while they are all types of endothelial cells, the specific morphologies, biological characteristics and effects the cells would potentially exert on any given tissue would require individual considerations. Finally, the disclosed species of tissues or organs to which the cells are administered do not, in contrast to Applicant's statement, share the common characteristic of requiring vascularization for growth and survival; particularly it is noted that cartilage (one of the claimed species) is a non-vascularized tissue type. Therefore, as a whole, the disclosed species cannot be considered art-recognized equivalents, even with regards to their vascularization requirements, because each of the claimed tissue types has individual microvascular structures (or none at all, in the case of cartilage), and thus would be treated differently.

Therefore, the requirement is still deemed proper and is therefore made FINAL.

Claims 1-28 and 79-86 remain pending in the current application. Claims 5, 6, 19 and 23 are withdrawn pursuant to 37 CFR 1.142(b) as being directed to non-elected species of the instant invention, there being no allowable generic or linking claim. Claims 1-4, 7, 9-18, 20-22, 25-28 and 79-86 have been considered on the merits.

Priority

Acknowledgement is made that the instant application is a national stage entry under 35 USC 371 of international application PCT/US03/34838, filed 10/30/2003, which further claims priority under 35 USC 119(e) to US provisional application 60/422,709, filed 10/31/2002.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 2 and 4 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Applicants' claim 1 is directed to a method for inducing blood vessel formation or engineering blood vessels in a tissue or organ of a mammal, said method comprising administering perivascular cells (elected species) to a tissue or organ of a mammal in need of increased blood vessel formation or engineered blood vessels.

Dependent claim 2 requires said mammal to have a deficiency of at least 5% of a particular cell type. Claim 2 is rejected as indefinite because it is unclear if the particular cell type, of which there is a deficiency, are the same as those cells which are administered in claim 1. Specifically, it is unclear if perivascular cells (elected species of claim 1), are the cells which said mammal has at least a 5% deficiency of. If not, it is unclear how the deficiency noted claim 2 relates to the method of claim 1.

Dependent claim 4 requires mammal has a disease, disorder or condition wherein said administration of cells provides a dose of cells sufficient to ameliorate or stabilize said disease, disorder or condition. Claim 4 is rejected as indefinite because it is not clear if the disease, disorder or condition is necessarily related to the need of increased blood vessel formation or engineered blood vessels. Claim 4

does not define the disease, disorder or condition in any way, thus the relationship between the disease, disorder or condition of claim 4 and the effect achieved by the method of claim 1 is unclear.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-4, 7, 9-18, 20-22, 25-28 and 79-86 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

Analysis of whether a particular claim is supported by the disclosure in an application requires a determination of whether that disclosure, when filed, contained sufficient information regarding the subject matter of the claims as to enable one skilled in the pertinent art to make and use the claimed invention without undue or unreasonable experimentation. See *Mineral Separation v. Hyde*, 242 U.S. 261, 270 (1916). The key word is 'undue,' not experimentation.' " (Wands, 8 USPQ2d 1404). The factors to be considered in determining whether undue experimentation is required are summarized In re Wands 858 F.2d 731, 8 USPQ2nd 1400 (Fed. Cir, 1988). The factors to be considered in determining whether undue experimentation is required include: (1) the quantity of experimentation necessary, (2) the amount or direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims. While all these factors are considered, a sufficient number are discussed below so as to create a prima facie case.

Applicants' claims are directed to methods for inducing or increasing blood vessel formation or engineering blood vessels in a tissue or organ of a mammal, comprising administering perivascular cells to a tissue or organ of a mammal in need of increased blood vessel formation or engineered blood vessels. Some dependent claims require the method to comprise further administration of an additional endothelial cell type or endothelial precursor cell type, specifically HUVEC. Other dependent claims recite effects of the method, such as increasing cell number and/or biological activity of cells within the tissue by at least 5%. Other dependent claims require the cells to be administered as part of a matrix or scaffolding.

At the time the invention was made it was known that two types of cells were involved in development of the vascular system: endothelial cells and perivascular cells, however the majority of research had been focused on endothelial cells (ECs), little was known about perivascular cells and their role in blood vessel formation (See Hellstrom et al, 1999, Pg. 3047). Perivascular cells is a generic term which refers to the cells of the media of blood vessels, depending on the vessel type (large versus small vessels), the perivascular cell comprise vascular smooth muscle cells (vSMCs) or pericytes (PCs), respectively (See Hirschi et al, 1998, Pg. 805).

While there was evidence that perivascular cells were present in blood vessels (See Hirschi et al, 1998, Pg. 812-813), the skilled artisans had not reached a consensus with regards to the role perivascular cells played in development of new blood vessels via angiogenesis and/or vasculogenesis. In fact, there were conflicting views, each supported by evidence, regarding the role of perivascular cells in blood vessel formation. Benjamin et al asserted pericyte recruitment lags behind EC sprouting in the angiogenic process (See Benjamin et al, 1999). Benjamin et al work on retinal angiogenesis, and report ECs form the initial vascular network and then recruit pericytes, only upon recruitment of the pericytes do the vessels stabilize and mature. Alternatively, Amselgruber et al assert pericytes are the 'pioneer' cells in the angiogenic sprouting process, going before the EC into new cellular territory (See Amselgruber et al,

1999). Amselbruger et al work on angiogenesis in the corpus luteum, where pericytes are found to the be first vascular cells to invade the granulose folds of the ruptured follicles and function as guides for subsequent outgrowth of ECs into the corpus luteum. The conflicting views presented in the art are taken to show the state of the art was unpredictable at the time of filing.

It has been held that the amount of guidance or direction needed to enable the invention is inversely related to the amount of knowledge in the state of the art as well as the predictability in the art. *In re Fisher*, 427 F.2d 833, 839, 166 USPQ 18, 24 (CCPA 1970). The "amount of guidance or direction" refers to that information in the application, as originally filed, that teaches exactly how to make or use the invention. The more that is known in the prior art about the nature of the invention, how to make, and how to use the invention, and the more predictable the art is, the less information needs to be explicitly stated in the specification. In contrast, if little is known in the prior art about the nature of the invention and the art is unpredictable, the specification would need more detail as to how to make and use the invention in order to be enabling. See, e.g., *Chiron Corp. v. Genentech Inc.*, 363 F.3d 1247, 1254, 70 USPQ2d 1321, 1326 (Fed. Cir. 2004).

In the instant case, it has been shown that there was little consensus in the art regarding the role of perivascular cells in vasculature formation. There is no experimental evidence in the art regarding administration of perivascular cells, either alone or in combination with endothelial cells, into a tissue or organ to induce or otherwise modulate vasculature formation, as currently claimed. Therefore, in order to enable for the invention as currently claimed, the specification would need to provide a high level of teachings and guidance as to how to successfully carry out the method of the current inventions to achieve the desired effects. However, the amount of guidance in the specification is not found sufficient to enable one of ordinary skill to successfully carry out the method as currently claimed.

The working examples provided in the specification are limited to the ability of preadipocytes to induce angiogenesis *in vivo*. The first example shows preadipocytes administered as a fat pad on the

backs of mice to differentiate and support formation of an immature vasculature (evidence of angiogenesis). The second example shows HUVEC-seeded constructs co-cultured *in vitro* with preadipocytes or mesenchymal precursor cells, then implanted into mice supported formation of an immature vasculature *in vivo*. It is noted that the 10T1/2 cells which were used as mesenchymal precursor cells are also precursors of perivascular cells, however they are not perivascular cells, per se, only precursors thereof, and thus are not representative of the invention as claimed. Therefore, the evidence provided in the specification is limited to induction of blood vessel formation by administration of preadipocytes, which is not the currently elected species of the instant claims. Disclosure of blood vessel formation by administration of perivascular cells is limited to a statement in the specification that perivascular cells may be administered (See Specification, e.g. Pg. 2). No specific discussion or teachings with regards to this cell type is presented in the specification.

The Examiner acknowledges that the Office does not require the presence of working examples to be present in the disclosure of the invention (see MPEP §2164.02). However, in light of the high level of unpredictability in the art, highlighted by a lack of consensus regarded the roles of perivascular cells in vascular formation, the Office would require appropriate disclosure to provide the artisan with a reasonable expectation of successfully carrying out the method as claimed. Since the present specification would not enable the skilled artisan to prevent hypertension, a clear burden of undue experimentation would be placed upon the skilled artisan in order to practice the invention.

As the cited art and discussion of the above 8 factors establish, practicing the claimed method in the manner disclosed by Applicant would not imbue the skilled artisan with a reasonable expectation that induction of blood vessel formation, or increasing blood vessel formation by the method of the instant claims could be achieved. Given that the art fails to recognize and Applicant has failed to demonstrate that perivascular cells have an appreciable, and controlled effect on blood vessel formation, the skilled

artisan would be faced with the impermissible burden of undue experimentation in order to practice this embodiment of the claimed invention. Accordingly, all claims are deemed properly rejected.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to ALLISON M. FORD whose telephone number is (571)272-2936. The examiner can normally be reached on 8:00-6 M-Th.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Michael Wityshyn can be reached on 571-272-0926. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Allison M. Ford/
Examiner, Art Unit 1651